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# Original article

## Menstrual cycle and timing of breast surgery in premenopausal node-positive breast cancer: Results of the International Breast Cancer Study Group (IBCSG) Trial VI

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**Summary**

*Purpose:* It has been postulated that breast cancer surgery performed during the follicular phase of the menstrual cycle is associated with poorer outcome.

*Patients and methods:* We tested this hypothesis by evaluating disease-free survival (DFS) for 1033 premenopausal patients who received definitive surgery either during the follicular phase ($n$ = 358) or the luteal phase ($n$ = 675). All patients were enrolled in a randomized trial conducted between July 1986 and April 1993. All had node positive breast cancer and randomization was stratified by estrogen receptor (ER) status. All patients received at least three cycles of adjuvant cyclophosphamide, methotrexate, and 5-fluorouracil (CMF). The median follow-up was 60 months.

*Results:* Patients who underwent definitive surgery for breast cancer in the follicular phase had a slightly worse disease-free survival than those operated on during the luteal phase (five-year DFS percentage: 53% *versus* 58%; hazard ratio, 1.13; 95% confidence interval (CI), 0.94–1.38; $P$ = 0.20). The effect was significantly greater for the subpopulation of 300 patients with ER-negative primaries ($P$ = 0.02 interaction effect; five-year DFS percentages 42% vs. 59%; hazard ratio 1.60; 95% CI, 1.12–2.25; $P$ = 0.008). The effect of timing of surgery diminished for analyses based on lesser surgical procedures, e.g., excisional biopsies. In particular, no effect of timing was observed for fine needle aspiration procedures.

*Conclusions:* Surgical procedures which are more extensive than a fine needle aspiration biopsy might be associated with worse prognosis if conducted during the follicular phase of the menstrual cycle. This phenomenon was seen predominantly for high risk breast cancer with low levels or no estrogen receptors in the primary tumor.

**Key words**: adjuvant chemotherapy, breast cancer, menstrual cycle, premenopausal, surgery

### Introduction

The timing of surgery within the various phases of the menstrual cycle was hypothesized to influence disease-free survival and overall survival for patients with operable breast cancer. However, the data from various retrospective analyses of this aspect provide conflicting results [1, 2]. The first report that premenopausal women who are operated during the follicular phase have a significantly worse prognosis when compared with those operated during the luteal phase was based upon a cohort of 41 patients [3]. This observation was confirmed by some investigators [4–7], while others did not find a significant difference in prognosis according to whether the operation took place in the follicular or in the luteal phase [8–10]. In the largest series in which a difference was observed [7], its magnitude was greater for patients with node-positive disease. The relationship of the extent of a surgical procedure to the menstrual phase [11] is also controversial. We, therefore, systematically collected data on the menstrual phase for patients with node-positive breast cancer who entered a randomized trial in which all received CMF adjuvant chemotherapy without the addition of endocrine manipulations. Furthermore, we recorded all surgical procedures which were associated with the diagnosis and treatment of the disease [12].

### Patients and methods

Data from International Breast Cancer Study Group (IBCSG) trial VI [12], which accrued 1554 pre- and perimenopausal patients from July 1986 to April 1993 were considered for the analysis. All patients had a histologically proven, node positive unilateral breast cancer with either estrogen receptor (ER) positive or negative status. Surgery of the primary tumor was either a total mastectomy with axillary clearance or a breast conserving procedure (quadrantectomy or lumpectomy) with axillary lymph node clearance and subsequent local radiotherapy. Patients received one of the following: A) cyclophosphamide, methotrexate, and fluorouracil for six consecutive courses on months 1 to 6 (CMF × 6); B) CMF × 6 plus three single courses of reintroduction CMF given on months 9, 12, and 15; C) CMF for three consecutive courses on months 1 to 3 (CMF × 3); or D) CMF × 3 plus three single

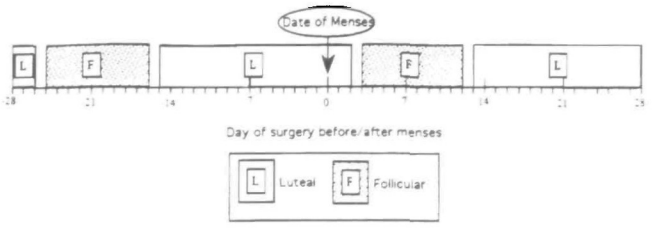


*Figure 1.* Date of most recent menses prior to entry into the trial and estimation of menstrual phase.

courses of reintroduction CMF given on months 6, 9, and 12. Seventy-five percent of the patients were randomized to receive at least six cycles of CMF. Trial details, eligibility and evaluation, as well as results at 60 months median follow-up are described elsewhere [12]. For this analysis, the timing of definitive surgery (total mastectomy, or lumpectomy or quadrantectomy) in relation to a woman's menstrual cycle was considered (definition A). When each patient enrolled in the trial we asked 'date start of most recent menstruation (prior to date of randomization)'. We refer to this as 'menses date' in this paper. If definitive surgery was between 3 and 12 days (inclusive) following menses date, or between 16 and 25 days prior to menses date, then surgery was said to be performed during the follicular phase. If definitive surgery was between 0 and 2 or 13 and 28 days following recent menses date, or between 1 and 15 or 26 and 28 days prior to menses date, then surgery was said to be performed during the luteal phase (Figure 1). Patients who had a hysterectomy ($n$ = 106), had surgery performed beyond 28 days of last menses ($n$ = 233), or had an incomplete menses date, making it impossible to classify the timing of surgery ($n$ = 103), were excluded from the analysis. Of the 1475 eligible patients from trial VI, 1033 had sufficient data to be included in this analysis (Table 1).

To evaluate whether surgeries of lesser extent have a similar influence on the results, we considered two additional analyses. In the first, the date of surgical procedure was the date of definitive surgery or the date of a diagnostic procedure which was more intrusive than fine needle aspiration (trucut, incisional, or excisional biopsy), whichever was performed first ($n$ = 1016, definition B, Table 1). In the second analysis, the date of surgery was the date of fine needle aspiration. This analysis was restricted to only those patients who had this less intrusive procedure ($n$ = 465, definition C, Table 1). For both of these analyses, menses phase was determined as described previously for definition A.

ER subgroups were also considered within each of the definitions since ER status was a stratification factor in trial VI and ER status has been an important factor in predicting response to endocrine therapies.

Disease-free survival (DFS) was defined as the length of the time from the date of randomization to any relapse (including ipsilateral breast recurrence), the appearance of a second primary cancer (including contralateral breast cancer), or death, whichever occurred first. The Kaplan–Meier method was used to estimate survival distributions for DFS [13]. The two-sided log-rank procedure was used to assess the statistical significance of treatment differences between the survival distributions [14]. Multivariate analyses were conducted using Cox proportional hazards regression models [15]. The data were analyzed at a median observation time of 60 months, and five-year DFS percentages are presented.

*Table 1.* Reasons for exclusion of patients from timing of surgery analysis.

| | Definition[a] | | |
|---|---|---|---|
| | A | B | C |
| Total eligible | 1475 | 1475 | 1475 |
| Evaluable | 1033 | 1016 | 465 |
| Not evaluable | | | |
| Did not receive fine needle aspiration | – | – | 727 |
| Missing 'method of diagnosis' date | – | 4 | 13 |
| Hysterectomy | 106 | 106 | 40 |
| Surgery beyond 28 days of menses | 233 | 246 | 180 |
| Incomplete menses date[b] | 103 | 103 | 50 |

[a] Definition A: timing of definitive surgery; definition B: timing of first invasive procedure; definition C: timing of fine needle aspiration.
[b] Includes patients with incomplete date of last menses (primarily missing day only) who could not be classified as having the target procedure (definition A, B, C) beyond 28 days of menses.

## Results

The first analysis included 1033 patients out of the 1475 women randomized in trial VI. Overall there was no significant difference in the disease-free survival between the groups operated on in the two distinct phases of the menstrual cycle (Figure 2a; log-rank $P$ = 0.20). Evaluating the results separately for the two prospectively stratified subgroups, there was an effect among patients with estrogen receptor-negative tumors, while no effect was observed for patients with estrogen receptor-positive

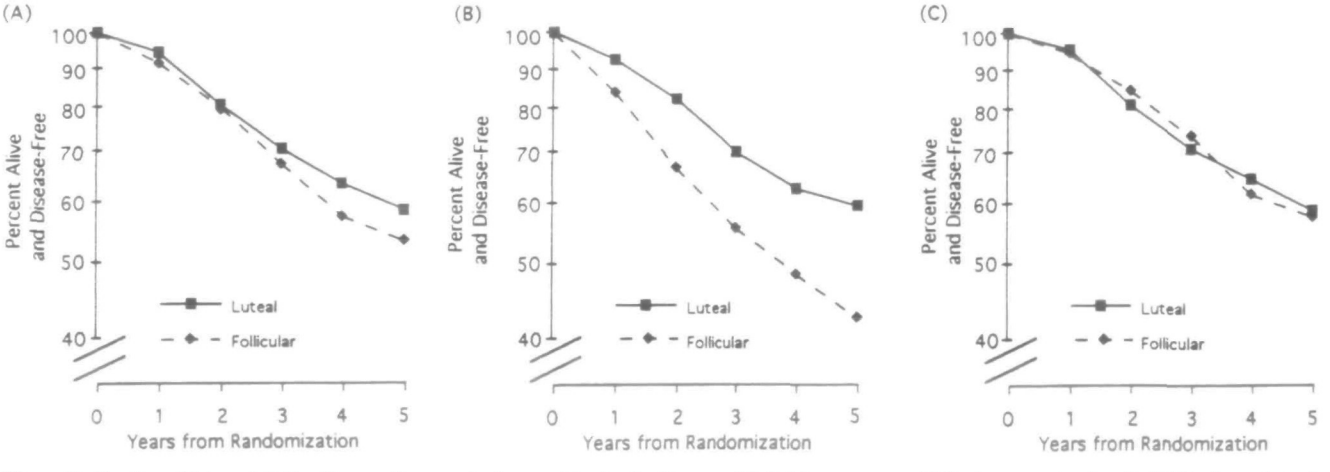


*Figure 2.* Kaplan–Meier plots for disease-free survival according to the timing of definitive surgery within the menstrual cycle (follicular or luteal phase) for premenopausal patients with node-positive breast cancer in IBCSG Trial VI (12): all patients ($n$ = 1033, panel A), patients with estrogen receptor-negative tumors ($n$ = 300, panel B), or patients with estrogen receptor-positive tumors ($n$ = 733, panel C).

*Table 2* Estimated five-year DFS percentages and hazard ratios according to menses phase for definition A.

| Patient population menses phase | *n* | Five-year DFS (%) | HR | 95% CI | *P*-value |
|---|---|---|---|---|---|
| All patients (definition A) | | | | | |
| Follicular | 358 | 53 | 1.13 | 0.94, 1.38 | 0.20 |
| Luteal | 675 | 58 | | | |
| ER-negative | | | | | |
| Follicular | 108 | 42 | 1.60 | 1.12, 2.25 | 0.008 |
| Luteal | 192 | 59 | | | |
| ER-positive | | | | | |
| Follicular | 250 | 57 | 0.98 | 0.77, 1.24 | 0.86 |
| Luteal | 483 | 58 | | | |
| Mastectomy (definition A) | | | | | |
| Follicular | 245 | 49 | 1.07 | 0.86, 1.35 | 0.52 |
| Luteal | 470 | 53 | | | |
| ER-negative | | | | | |
| Follicular | 72 | 38 | 1.62 | 1.08, 2.43 | 0.02 |
| Luteal | 137 | 58 | | | |
| ER-positive | | | | | |
| Follicular | 173 | 53 | 0.93 | 0.70, 1.19 | 0.51 |
| Luteal | 333 | 51 | | | |
| Less than mastectomy (definition A) | | | | | |
| Follicular | 113 | 62 | 1.41 | 0.93, 2.12 | 0.11 |
| Luteal | 205 | 70 | | | |
| ER-negative | | | | | |
| Follicular | 36 | 49 | 1.57 | 0.80, 3.08 | 0.18 |
| Luteal | 55 | 60 | | | |
| ER-positive | | | | | |
| Follicular | 77 | 68 | 1 24 | 0.73, 2.11 | 0.43 |
| Luteal | 150 | 73 | | | |

Abbreviations: *n* – number of patients; DFS – disease-free survival; HR – hazard ratio, follicular: luteal; 95% CI – 95% confidence interval; ER – estrogen receptor.

tumors (Figures 2b and 2c, respectively; test for interaction $P = 0.02$). Patients with estrogen receptor-negative tumors whose operation was performed during the follicular phase had a five-year disease-free survival of 42% compared with 59% for those operated on during the luteal phase (hazard ratio 1.6; 95% CI 1.12–2.25; $P = 0.008$). In contrast, patients with estrogen receptor-positive tumors had five-year disease-free survival of 57% and 58% if operated on during the follicular or luteal phase, respectively.

To investigate whether the results were influenced by the extent of definitive surgery, we evaluated the outcome separately for patients who received a mastectomy or less than mastectomy. For the patients who received a mastectomy ($n = 715$), the results were similar. Overall there was no significant difference in disease-free survival between the two menses categories (log-rank $P = 0.52$). Again, an effect between menses categories was only found for the patients with estrogen receptor-negative tumors (test for interaction $P = 0.02$). For the patients who received less than mastectomy ($n = 318$), no effect was found overall or within estrogen receptor subgroups (test for interaction $P = 0.56$). Table 2 presents the estimated five-year disease-free survival percentages, hazard ratios, and *P*-values for the results according to timing of definitive surgery.

*Table 3.* Estimated five-year DFS percentages and hazard ratios according to menses phase for definition B and C.

| Menses phase | *n* | Five-year DFS (%) | HR | 95% CI | *P*-value |
|---|---|---|---|---|---|
| Definition B | | | | | |
| Follicular | 348 | 55 | 1.03 | 0.85, 1.26 | 0.74 |
| Luteal | 668 | 57 | | | |
| ER-negative | | | | | |
| Follicular | 105 | 47 | 1.19 | 0.84, 1.71 | 0.32 |
| Luteal | 194 | 55 | | | |
| ER-positive | | | | | |
| Follicular | 243 | 58 | 0.96 | 0 76, 1.23 | 0.77 |
| Luteal | 474 | 57 | | | |
| Definition C | | | | | |
| Follicular | 185 | 55 | 1.01 | 0.76, 1.35 | 0.93 |
| Luteal | 280 | 57 | | | |
| ER-negative | | | | | |
| Follicular | 67 | 52 | 0.92 | 0.57, 1.50 | 0.71 |
| Luteal | 96 | 53 | | | |
| ER-positive | | | | | |
| Follicular | 118 | 56 | 1.07 | 0.75, 1.55 | 0.70 |
| Luteal | 184 | 59 | | | |

Abbreviations: see Table 2.

The second analysis included 1016 patients and was based on date of first surgical procedure including any type of surgery defined as more intrusive than a fine needle aspiration. Of the women 217 (22%) received either a trucut, incisional, or excisional biopsy. Again there was no significant difference in the disease-free survival between the groups operated on in the two distinct phases of the menstrual cycle (log-rank $P = 0.74$). Evaluating the results separately for the two prospectively stratified subgroups, the difference in effects between the estrogen receptor-negative and estrogen receptor-positive cohorts was no longer statistically significant (test for interaction $P = 0.31$). Table 3 presents the estimated five-year disease-free survival percentages, hazard ratios, and *P*-values for these analyses.

The third analysis included 465 patients for whom a fine needle biopsy was performed for cytology. There was no difference in disease-free survival between the groups operated on in the two distinct phases of the menstrual cycle either overall (log-rank $P = 0.93$), or for subpopulations defined by estrogen receptor content of the primary tumor. Table 3 presents the results of these analyses.

Multivariate analyses using proportional hazards regression models were conducted to adjust for effects of estrogen receptor status (positive vs. negative), number of positive nodes ($\geq 4$ vs. 1–3), age ($\geq 40$ vs. $< 40$ years), tumor size ($> 2$ vs. $\leq 2$ cm), tumor grade (III vs. other; unknown vs. other), vessel invasion (yes vs. unknown; no vs. unknown), and treatment (CMF × 3 vs. other).

The conclusions based on these models are the same as those based on the univariate analyses shown in Tables 2 and 3. The effect of timing of surgery remained statistically significant for the patients with ER negative primaries.

## Discussion

The timing of surgery within various phases of the menstrual cycle was hypothesized to influence prognosis of premenopausal patients with breast cancer. Surgery during the follicular phase was thought to be unfavorable when compared with surgery during the luteal phase [1]. The tissue trauma due to surgery is known to enhance biological processes that may stimulate tumor growth [16]. In studies conducted on the production of growth factors by surgically traumatized tissues, an increased production of TGF-α was observed at the wound site [17]. It is known that estrogens may lead to an increased production of TGF-α by the stroma and by estrogen receptor containing tumor cells [18]. Estrogens may cause a greater susceptibility to the effects of growth factors on tumor cells which are rapidly proliferating; for example, those which do not contain estrogen receptors [19]. The presence of progesterone, naturally available during the luteal phase, might slow this tumor cell proliferation. Increased availability of progesterone was hypothesized to be associated with improved outcome for women operated during the luteal phase [20]. Mechanisms related to invasion, metastatic potential and angiogenesis might also be affected differently in the absence or presence of progesterone [21, 22].

Several features distinguish our study population from other series that addressed the timing of surgery and menstrual cycle. All patients had node-positive disease, all received CMF adjuvant chemotherapy, and all had estrogen receptor data available prior to study entry. We also conducted three different analyses defined according to the extent of surgery used. The magnitude of the decrease in disease-free survival associated with surgery during the follicular phase was reduced as the extent of the surgical intervention decreased. We also observed that the effect of the timing of surgery was most striking for patients with estrogen receptor negative tumors.

For the premenopausal patient the definition of an estrogen receptor-negative tumor is confounded by the presence of circulating estrogens and by changes in expression of steroid hormone receptors during the menstrual cycle [23]. It should also be recognized that there is a lack of precision in determining the phase of the cycle. We did not measure hormone levels at the time of surgery. Nevertheless, this is the first time that we have observed an effect of the timing of surgery within the phase of the menstrual cycle. Although the results of the subgroup analyses should be treated with caution, there is some biologic rational for observing the effect in the subpopulation of patients with estrogen receptor-negative tumors. Such tumors have a more rapid cell proliferation and are associated with a higher risk of relapse despite adjuvant chemotherapy. An association between timing of surgery in the menstrual cycle and outcome among patients with estrogen receptor-negative tumors was also observed by Saad et al. [24].

Before analysis we recorded the hypothesis that the largest effect would be seen in patients with estrogen receptor-negative tumors. Our data supported this hypothesis.

We identified the patients having tumors with the highest proliferative potential and the worst prognosis as those whose clinical course was most strongly associated with the timing of the surgical procedure. However, this is the very population of patients whose outcome might be adversely affected by delaying surgical intervention to await the luteal phase of the cycle. Alternative interventions should therefore be considered to reduce tumor cell proliferation and/or alter the hormonal status of the host in such patients. Patient selection for these procedures requires pre-operative evaluation. A potential advantage of pre-operative chemotherapy, currently being evaluated in randomized clinical trials, might be seen particularly in those patients with rapidly proliferating tumors who undergo invasive surgical procedures during the follicular phase.

Although the IBCSG has not yet investigated preoperative chemotherapy, our trial of perioperative chemotherapy [25] supports the idea that such treatment may be more effective in patients with estrogen receptor-negative tumors. Thus, among 168 premenopausal patients with estrogen receptor-negative tumors, there was a trend toward superior five-year disease-free survival for patients commencing therapy in the perioperative period (55% ± 5%) compared with those receiving only conventionally timed therapy (44% ± 4%; $P = 0.39$). No such trend was seen among patients with estrogen receptor-positive tumors.

These results highlight the importance of considering tumor and host factors when developing optimal integrated strategies for management of early breast cancer.

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## *Appendix

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